Reviewers: Brenda MacDonald, Gordon Cockell, Date: November 26, 1999
Supplemental data reviewer: Gordon Cockell, Date: November 26, 1999

STUDY TYPE: Multigeneration Reproduction Study - Rat, OPPTS 870.3800 (§83-4); OECD 416.

TEST MATERIAL (PURITY): CGA 293343 Technical, 98.6%

SYNONYMS: Thiamethoxam

CITATION: Winkler, G., Doubovetzky, Dr. M., (1998). CGA 293343 Technical: Rat Dietary Two-Generation Reproduction Study. Novartis Crop Protection AG, Toxicology, Stein, Switzerland, Study no. 942121, July 20, 1998. Unpublished. MRID 44718707.

SPONSOR: Novartis Crop Protection AG, Human Safety Assessment, Basel, Switzerland.

EXECUTIVE SUMMARY: In a 2-generation reproduction study, CGA 293343, purity 98.6%, was administered to 30 Tif: RAI f (SPF) rats/sex/dose in the diet at concentrations of 0, 10, 30, 1000 and 2500 ppm (equal to 0, 0.61, 1.84, 61.25 and 158.32 mg/kg bw/day for males, and 0, 0.80, 2.37, 79.20 and 202.06 mg/kg bw/day for females). Each female in each generation was mated to produce two litters.

For the parental animals, body weight gain was slightly lower in the 2500 ppm group during the first 6 weeks of the study, F_0 and F_1 generations, males only. However, the effect was marginal and was not considered to be toxicologically significant. Decreased testis weight was observed in the F_1 generation at 2500 ppm, and increased incidence and severity of tubular atrophy was observed in the testes in the F_1 generation at 30 ppm and above. Sperm motility was decreased in all treatment groups in both generations, however, there was no dose-response relationship, there was high variability among all groups and there were no treatment-related effects on sperm count or sperm morphology. A separate, complementary study was conducted to investigate this finding. On the basis of the special investigation, it was concluded that the initial findings were likely due to technical error and not related to treatment with CGA 293343. The supplemental information was limited to analysis of F_0 animals, hence no information relevant to the findings in F_1 animals is available. Increased incidence of hyaline changes was observed in the renal tubules for F_0 and F_1 males in the 1000 and 2500 ppm groups, and an increased incidence of renal tubular casts was noted for F_0 males in the 1000 ppm group, and F_0 and F_1 males in the 2500 ppm group. Hyaline change in renal tubules was also observed in one F_1 female at 2500 ppm. A slight increase in food consumption was observed in F_1 females during gestation with the F_{1a} and F_{1b} litters, but this was not considered to be toxicologically significant.

For offspring, body weight gain was lower in the 2500 ppm group during the lactation period in the F_{1a}, F_{1b}, F_{2a} and F_{2b} litters, both sexes, resulting in lower body weights on days 7, 14 and/or 21 postpartum. Slightly lower body weight gain and body weights (days 7, 14 and/or 21 postpartum) were also noted in the 1000 ppm group for F_{2a} and F_{2b} females. However, the effect was marginal (≤8% lower than the control group values), F_{1a} and F_{1b} pups were not affected and males were not affected, and so this finding was not considered to be toxicologically significant.

In males, the reproductive toxicity LOAEL is 30 ppm (1.8 mg/kg bw/day) based on increased incidence and severity of tubular atrophy observed in testes of the F_1 generation; the NOAEL is 10

ppm (0.6 mg/kg bw/day). There were no adverse, treatment-related effects on reproductive parameters (mating, gestation, fertility, viability) noted at any dose level tested, **therefore, the NOAEL for reproductive toxicity in females is 2500 ppm (202 mg/kg bw/day).**

For parental systemic toxicity, the LOAEL for males is 1000 ppm (61 mg/kg bw/day), based on increased incidence of hyaline change in renal tubules in F_0 and F_1 animals. The NOAEL is 30 ppm (1.8 mg/kg bw/day). The NOAEL for females is 2500 ppm (202 mg/kg bw/day, the highest dose tested) based on a slight increase in food consumption for F_1 females during gestation with the F_{1a} and F_{1b} litters which was not considered to be toxicologically significant.

For offspring toxicity, the LOAEL is 2500 ppm (158 mg/kg bw/day for males, and 202 mg/kg bw/day for females) based on reduced body weight gain during the lactation period in all litters. The NOAEL is 1000 ppm (61 mg/kg bw/day in males and 79 mg/kg bw/day in females).

The reproductive study in the rat is classified as acceptable and satisfies the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800, §83-4); OECD 416 in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1 Test Material: CGA 293343

Description:	Technical material; further details not provided
Lot/Batch #:	P.506006
Purity:	98.6 % a.i.
Compound Stability:	Not given; stated to be the responsibility of the sponsor
CAS #:	53719-23-4

2. Vehicle: N/A; test material administered in the diet

3 Test Animals:

Species:	Rat	
Strain:	Tif: RAI f (SPF), hybrids of RII/1 x RII/2	
Age at start of dosing:	(F_0) 6 to 7 weeks; (F_1) 6 to 7 weeks	
Wt. at study initiation:	(F_0) Males 150.2 g to 256.0 g; Females 118.2 g to 182.3 g (F_1) Males 57.8 g to 213.6 g; Females 59.8 g to 192.2 g	
Source:	Laboratory Animal Breeding, CIBA-GEIGY Ltd., Stein, Switzerland	
Housing:	Individually in Macrolon Type 3 cages with granulated soft wood bedding	
Diet:	Pelleted, certified standard feed (Nafag No. 890) *ad libitum*	
Water:	Tap water *ad libitum*	
Environmental conditions:	**Temperature:**	22±3°C
	Humidity:	50±20%
	Air changes:	~ 16/hr
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	At least 7 days prior to initiation of treatment	

B. PROCEDURES AND STUDY DESIGN

1. In-Life Dates: November 6, 1995 to September 23, 1996.

2. Mating Procedure: Females were mated with males from the same test group, 1:1 ratio, until successful mating occurred, or for 19 days (whichever came first). Animals which did not mate were sacrificed and necropsied. Mating was confirmed by the presence of a vaginal plug or the presence of sperm in a vaginal smear, and was designated as day 0 of gestation. After successful mating, each pregnant female was individually placed into a cage with soft wood bedding where it was kept through gestation and lactation. Both the F_0 and F_1 generations were mated to produce 2 litters each, F_{1a} and F_{1b}, and F_{2a} and F_{2b}, respectively. Sibling matings within the F_1 generation were avoided.

3. Study Schedule: Starting at 6 to 7 weeks of age, F_0 generation animals were given test diets for 10 weeks before they were mated. Upon weaning at 3 weeks of age, F_{1a} pups were selected to become parents of the F_1 generation and were given the same concentration of test diet as their dam. F_{1a} animals were given test diets 10 weeks prior to mating. F_0 generation animals were mated 4 weeks after weaning of the F_{1a} pups to produce the F_{1b} pups. All animals were fed the test diets continuously throughout the study period.

4. Animal Assignment: F_0 animals were randomly assigned to test groups using a computer-generated randomization schedule with stratification by body weight, as seen in Table 1.

TABLE 1 Animal Assignment

Test Group	Dose in Diet[a] (ppm)	Animals/group			
		P Males	P Females	F_1 Males	F_1 Females
Control	0	30	30	30	30
Low Dose	10	30	30	30	30
Low-Mid Dose	30	30	30	30	30
Mid-High Dose	1000	30	30	30	30
High Dose	2500	30	30	30	30

a Diets were administered from beginning of the study until sacrifice

5. Dose Selection Rationale: Dose levels were chosen based on the results of:
I) a range finding reproduction study in rats, study no. 942120; and,
ii) a 90-day dietary toxicity study in rats, study no. 942089.
Based on the results of these studies, the dose levels chosen for the 2-generation rat reproduction study were considered appropriate by the reviewer.

6. Dosage Preparation and Analysis:

Fresh diets were prepared every 3 to 5 weeks throughout the study period by mixing appropriate amounts of test substance with ground feed pellets. Diets were stored at room temperature in unopened sacks or in polyurethane containers. Prior to the start of the study, stability of the test substance in feed mixtures was evaluated over a 5-week period stored at room temperature. In addition, stability (over a 5-week period) and homogeneity of mixing, were determined for all dose levels from samples (top, middle and bottom of mixer) taken at study initiation (i.e., first batch of test diet). Actual test material concentration in the diets was determined for all dose levels, from samples of test diets taken at study initiation, and then from every other batch of diet prepared throughout the study period.

Results:

Stability Analysis: The actual concentrations of CGA 293343 in the first batch of test diets, expressed as percentage of the nominal concentration, were as follows:

	Dose (ppm)				
Storage Interval	**0**	**10**	**30**	**1000**	**2500**
Day 0	-----	81.8%	95.6%	102.9%	102.7%
Day 35	-----	92.3%	98.6%	104.0%	102.6%

Based on these results, it was concluded that the test material was stable in pelleted feed for at least 5 weeks.

Homogeneity Analysis: Individual samples (i.e., from the top, middle and bottom of the mixer) of the test diets at concentrations of 10, 30, 1000 and 2500 ppm, varied by up to 6.6 %, 8.8%, 7.8 % and 2.8 %, respectively. These results are considered satisfactory for the purposes of this study.

Concentration Analysis: The range of values for the actual concentrations of CGA 293343 in the test diets, and the overall mean values, expressed as percentage of the nominal concentrations, were as follows:

	Dose (ppm)			
	10	**30**	**1000**	**2500**
Actual concentration, ppm				
Range of values	7.92 to 10.95	27.50 to 31.29	960.6 to 1108.0	2464 to 2797
Mean value	9.57	29.10	1022.0	2589
% of target concentration				
Range of values	79.2 to 109.5	91.7 to 104.3	96.1 to 110.8	98.6 to 111.9
Mean value	95.7	97.0	102.2	103.6

Based on these results, the actual test material concentrations, when compared to the target concentrations, were considered acceptable for the purposes of this study.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the study animals was acceptable.

C. OBSERVATIONS

1. Parental Animals: Animals were observed 1-2 times daily for mortality and clinical signs of toxicity. Individual body weights were measured on a weekly basis throughout the study. Food consumption values were recorded on a weekly basis at the same intervals used for recording body weights, except during cohabitation. From the body weight and food intake data, the mean daily food consumption per animal (g/animal/day) and the mean daily substance intake per animal (mg/kg bw/day) were calculated.

2. Litter Observations: On day 4 postpartum, all litters were culled by random selection to a maximum of 8 pups/litter (4/sex/litter, if possible); excess pups were killed by decapitation and necropsied.

Litter parameters measured and recorded were duration of gestation; the number of live and dead pups, and sex of pups on days 0, 4 (pre- and post-cull), 7, 14 and 21 post-partum; and individual pup body weight on days 0, 4 (pre-cull), 7, 14 and 21 post-partum.
Pups were examined daily for mortality and clinical signs of toxicity. In addition, the righting reflex was tested once a day for all pups on days 2, 3 and 4 postpartum; and the number of pups/litter with both eyes open was recorded on a daily basis to 100% occurrence.

3. Postmortem Observations:

1) Parental Animals: All surviving parental males were sacrificed after delivery of the last "b" litter sired. Maternal animals were sacrificed after necropsy of the last "b" litter. Method of sacrifice was via exsanguination while under carbon dioxide (F_0) or ether (F_1) anaesthesia. A gross postmortem examination was conducted on all parent animals, non-pregnant animals and those dying before scheduled sacrifice. At that time, the ovaries, testes, spleen, kidneys, heart, adrenals, liver, thymus and brain were weighed. The uteri of non-pregnant animals were stained by the Salewski method to determine if pregnancy had occurred. In addition, the left testes and epididymides from 15 randomly selected F_0 and F_1 males, at all

dose levels, were appropriately processed for sperm analysis (i.e., spermatid count, sperm motility and sperm morphology).

A complete tissue inventory from each animal was collected and preserved in neutral buffered 4% formalin. Histopathological examination was conducted on the following tissues:

I) For all control and high dose F_0 and F_1 animals: Ovaries, uterus, vagina, epididymides, prostate, seminal vesicle, testes (only one in males which were selected for sperm evaluation), pituitary gland, kidneys and all gross lesions.

ii) Ovaries in all non-pregnant, sperm positive, females.

iii) Testes, epididymides, seminal vesicle and prostate in all males which did not mate.

iv) Kidneys in all males at all dose levels.

v) Thymus from all F_1 females.

Based on the observed increase in the incidence of tubular atrophy in F1 testes, subsequent reevaluation of testis slides from F_0 and F_1 animals was conducted, and reported separately as an amendment to the study report. The results of this re-examination have been incorporated into the main review, and detailed evaluation of the findings in the amendment is presented in Appendix 2.

2) Offspring: The F_0 offspring not selected as parental animals and all F_1 offspring were sacrificed by carbon dioxide inhalation after weaning at 21 days of age (for F_{1a} pups, after weaning of the last litter). A gross postmortem examination was conducted on each of these pups, and on those culled, found dead or sacrificed moribund.

D. DATA ANALYSIS

1. Statistical Analyses: Statistical analyses conducted were as follows:
a) for continuous data, ANOVA followed by Dunnett's t-test;
b) for categorical data, Chi-Square test followed by Fisher's Exact test; and,
c) for non-parametric data, Kruskal-Wallis test followed by Dunn's test.
These statistical analyses were considered appropriate and acceptable by the reviewer.

Note: Only pregnant animals with a defined day of mating were included in the gestation summary tables, and only animals with a defined day of parturition were included in the lactation summary tables.

2. Indices:
a) **Reproductive Indices:** The following reproductive indices were calculated from breeding and parturition records of animals in the study:

Female Mating Index = (# of females confirmed to have mated/# of females paired) x 100
Male Mating Index = (# of males confirmed to have mated/# of males used for mating) x 100
Female Fertility (Pregnancy) Index = (# of females pregnant/# of females mated) x 100
Male Fertility Index = (# of males producing pregnant females/# males confirmed to have mated) x 100
Parturition Index = (# of females with births/# of pregnant females) x 100
Gestation Index = (# of females that delivered litters with viable pups/# of pregnant females) x 100

b) **Offspring Viability Indices:** The following viability indices were calculated from lactation records of litters in the study:

Pup Live birth Index = (# of pups born alive/# of pups delivered) x 100
Pup Viability Index = (# of pups alive on day 4/# of pups born live) x 100
Pup Lactation Index = (# of pups alive on day 14/# of pups alive on day 4) x 100

3. Historical Control Data: Historical control organ weight data were submitted with this study.

II. RESULTS

A. PARENTAL ANIMALS

1. Mortality:

I) **F_0 generation**: There were no treatment-related mortalities. One female in the 30 ppm group was sacrificed on day 15 of gestation (F_{1a} litter) due to dyspnea, salivation and piloerection, and one male in the 30 ppm group was sacrificed moribund on day 180. At necropsy, solid contents in the esophagus were noted for both animals. Additional findings observed in the female were dilatation and discoloured contents of the small intestine, and vaginal hemorrhage. All remaining animals survived the duration of the study period.

ii) **F_1 generation**: There were no treatment-related mortalities. One female in the 10 ppm group was sacrificed moribund on day 0 of lactation (F_{2b} litter) with piloerection and hunched posture; no abnormal findings were observed at necropsy. In the 2500 ppm group, one female was sacrificed moribund on day 21 of gestation (F_{2b} litter) with respiratory sounds, salivation and piloerection, and one male was sacrificed moribund on day 316. Findings at necropsy were solid contents in the esophagus, dilatation of the uterus and small spleen (female); and mottled liver and enlarged spleen (male).

Clinical Signs: There were no overt clinical signs of treatment-related toxicity in the F_0 and F_1 generation parent animals.

2. Body Weight and Body Weight Gain:

I) **F_0 generation:** Refer to Table 4.

Pre-mating: For males, mean body weight gain was lower in the 2500 ppm group during the first 6 weeks of the Pre-mating period resulting in a slightly lower mean final body weight, i.e., 94.5% of the control group value, and slightly lower overall mean body weight gain, i.e., 92% of control group value. This finding, although slight, was considered to reflect a marginal, treatment-related effect. The reviewer did not consider this finding to be toxicologically significant. Mean body weight and body weight gain were comparable amongst the 0, 10, 30 and 1000 ppm groups.

For females, mean body weight and body weight gain were comparable amongst the 0, 10, 30, 1000 and 2500 ppm groups during the Pre-mating period.

Gestation and Lactation: There were no treatment-related effects during the gestation and lactation periods.

TABLE 4: Body Weight and Food Consumption - Pre-mating[a]

Observations/study week	Dose Group (ppm)				
	Control	10	30	1000	2500
F_0 Generation Males - Pre-mating					
Mean body weight (g) Week 0	199.5±19.9	198.8±19.3	198.2±22.7	199.2±20.7	196.8±19.4
Week 6	417.4±27.5	411.6±31.9	408.6±48.8	401.5±34.9	383.9±34.5**
Week 12	460.5±30.8	457.2±36.0	456.7±51.2	456.3±39.0	440.1±48.1
Week 20	539.7±36.4	533.0±45.2	532.3±67.3	529.3±53.1	510.2±65.3
Week 28	578.1±39.9	566.9±46.5	562.3±70.1	557.2±60.5	546.5±76.8
Mean body weight gain (g) Weeks 0-6[b]	222	212.8	210.4	202.3	187.2
Weeks 6-20[b]	118.3	121.4	123.7	127.8	126.3
Weeks 0-20	340.3±31.0	334.2±33.9	334.1±49.3	330.1±40.7	313.5±53.1
Weeks 21-28	37.0±12.0	33.3±12.3	32.3±16.1	27.0±13.5	33.5±16.2
Mean food consumption, g/animal/day Weeks 0-16[b]	25.5	24.9	25.2	24.9	24.9
Weeks 20-24[b]	25.7	24.9	25.2	25.2	25.8
F_0 Generation Females - Pre-mating					
Mean body weight (g) Week 0	154.5±11.9	153.7±12.5	153.5±11.4	152.7±13.1	154.2±13.4
Week 5	241.2±15.7	245.5±20.8	246.5±17.2	240.5±18.8	240.5±22.4
Week 10	265.4±16.9	271.1±22.3	272.5±19.4	267.4±22.1	266.4±24.5
Mean body weight gain (g) Weeks 0-5[b]	86.7	91.8	93	87.7	86.3
Weeks 5-10[b]	24.3	25.5	25.9	26.9	26
Weeks 0-10	111.0±9.8	117.3±14.5	118.9±13.6	114.6±16.6	112.3±14.6
Mean food consumption, g/animal/day Weeks 0-10[b]	17.5	17.5	17.7	17.4	17.7

a Data extracted from pages 134 to 163 of the study report
[b] Standard deviations not available
* Statistically different from control, $p<0.05$; Dunnett test
** Statistically different from control, $p<0.01$; Dunnett test

ii) **F_1 generation:** Refer to Table 5.

Pre-mating: For males, Mean initial body weight was lower in the 2500 ppm group, reflecting the lower final body weight of the F_{1a} generation pups. Mean body weight gain was lower during the first 6 weeks of the Pre-mating period in the 2500 ppm group. However, the overall mean body weight gain and mean final body weights were comparable amongst all groups, and so it was concluded that there were no toxicologically significant treatment-related effects on body weight. For females, mean body weight and body weight gain were comparable amongst the 0, 10, 30, 1000 and 2500 ppm groups during the Pre-mating period.

Gestation and Lactation: There were no treatment-related effects during the gestation and lactation periods.

TABLE 5: Body Weight and Food Consumption - Pre-mating[a]

Observations/study week	Dose Group (ppm)				
	Control	10	30	1000	2500
F_1 Generation Males - Pre-mating					
Mean body weight (g), Week 0	162.0±24.0	153.2±32.8	163.3±24.5	161.6±25.0	147.8±23.0
Week 6	416.2±29.7	411.8±40.8	404.7±43.7	403.5±38.3	382.7±36.5**
Week 12	476.8±35.6	478.8±45.5	462.2±51.6	457.9±46.4	445.0±47.8*
Week 20	551.3±44.2	559.3±60.1	544.1±63.3	538.9±63.3	532.3±69.9
Week 28	603.8±48.5	612.2±68.1	598.2±69.9	588.8±75.1	589.2±85.8
Mean body weight gain (g), Weeks 0-6[b]	254.24	258.52	241.48	241.92	234.87
Weeks 6-20[b]	135.15	147.52	139.38	135.43	149.62
Weeks 0-20	389.4±35.0	406.0±60.8	380.9±58.8	377.4±53.5	384.5±65.9
Weeks 21-28	37.0±12.0	33.3±12.3	32.3±16.1	27.0±13.5	33.5±16.2
Mean food consumption, g/animal/day Weeks 0-16[b]	26.4	27	27.2	27.1	27.5
Weeks 20-24[b]	26.1	26.7	27.8	26.6	28
F_1 Generation Females - Pre-mating					
Mean body weight (g), Week 0	146.522.1	134.3±25.8	141.7±16.6	142.3±17.0	134.7±20.0
Week 5	257.4±24.5	247.7±20.8	248.6±22.2	249.5±20.1	242.8±22.9
Week 10	294.1±31.2	281.4±20.2	284.4±25.6	288.9±19.2	279.0±24.8
Mean body weight gain (g), Weeks 0-5[b]	110.9	113.46	106.93	107.19	108.08
Weeks 5-10[b]	32.97	34.97	35.92	37.54	39.77
Weeks 0-10	143.9±22.8	148.4±25.3	142.9±22.0	144.7±13.1	147.9±23.0
Mean food consumption, g/animal/day Pre-mating (weeks 0-10)[b]	19.2	19	19.2	19.5	20.1
First gestation (days 0 to 21)[a]	20.9	20.5	20.4	21.4	22.3
Second gestation (days 0 to 21)[a]	22.2	22.2	22.7	23	24.6

a Data extracted from pages 249 to 278 of the study report
[b] Standard deviations not available
* Statistically different from control, $p<0.05$; Dunnett test
** Statistically different from control, $p<0.01$; Dunnett test

3. Food Consumption:

I) **F_0 generation:** Refer to Table 4, page 8. For males, the study authors considered a slight decrease (~7.5% lower than control group value) in food consumption for males in the 2500 ppm group during study weeks 5 and 6 to be treatment-related. However, since this was an isolated occurrence, and overall mean food intake values were comparable amongst all groups, the reviewer does not consider this to be a treatment-related effect. For females, mean food intake was comparable amongst all groups during the Pre-mating, gestation and lactation periods.

ii) **F_1 generation:** Refer to Table 5, page 9. Slight increases in mean food intake in the 2500 ppm group, both sexes, were noted sporadically during the Pre-mating period (i.e., weeks 10, 15 and 16 for males, and weeks 2 and 9 for females), and were considered to be treatment-related by the author. However, since these were isolated occurrences, and since mean total food intake for the study period was comparable amongst all groups, the reviewer does not consider this to be a treatment-related effect. For females, slightly increased mean food intake during gestation with the F_{1a} and F_{1b} litters

(due to a statistically significant increase in food intake during weeks 1 and 2 of gestation) appeared to be treatment-related, but were not considered toxicologically significant.

4. **Test Substance Intake:** Based on food consumption, the nominal dietary concentrations and body weight, the doses expressed as mean daily mg test substance/kg body weight during the entire study period (males) and pre-mating period (females) for the F_0 and F_1 generations are presented in Table 6. The values for the F_0 generation are considered to be representative of the test substance intake for the entire study. **[Note**: These data were not included in the study report, so were calculated by the reviewer.]

TABLE 6: Mean test substance intake ranges (mg/kg body weight/day)[a]

	Male				Female			
	10	30	1000	2500	10	30	1000	2500
F_0	0.61	1.84	61.25	158.32	0.8	2.37	79.2	202.06
F_1	0.69	2.07	68.95	180.81	0.88	2.63	88.24	235.69

[a] Values calculated by the reviewer from data extracted from pages 104 to 107, and 1120 to 1131 of the study report

5. **Reproductive Function:**

a. Estrous Cycle Length and Periodicity: Vaginal smear data were not included in this submission. However, there were no indications of treatment-related effects on these parameters during the study.

b. Sperm Measures:

F_0 generation and F_1 generation: Sperm motility was decreased in all treatment groups for both generations, refer to Table 7. However, there was no dose-response relationship, variability was high among all groups (according to the study author, this was probably indicative of technical flaws - possibly due to lack of randomization of animal sacrifices), and there were no treatment-related effects on sperm count or sperm morphology. There were no treatment-related findings upon gross examination of the testes, and there were no indications of male fertility abnormalities noted during the study period. However, histopathological examination of the testes in the F_1 generation revealed a treatment-related increase in the incidence and severity of atrophy of the seminiferous tubules. In consideration of this, the toxicological significance of the decreased sperm motility, noted for both generations, was uncertain.

TABLE 7: Sperm Motility[a]

Observations	Dose Group (ppm)				
	Control	10	30	1000	2500
F_0 Generation					
Motile	146±43	109±29*	103±41**	112±31*	109±29*
Non-motile	54±43	91±29*	97±41**	88±31*	91±29*
Percent motility	73±21	55±15*	51±20*	56±16**	55±14*
F_1 Generation					
Motile	131±29	106±24*	112±24	120±23	107±22*
Non-motile	69±29	94±24*	88±24	80±23	93±22*
Percent motility	65±14	53±12*	55±14	60±11	53±11*

[a] Data extracted from pages 169 and 285 of the study report

* Statistically different from control, $p<0.05$; Dunnett test

** Statistically different from control, $p<0.01$; Dunnett test

Sperm analysis was repeated in a separate complementary study, study no. 982015, to determine if the above-noted finding of decreased sperm motility was related to treatment. Results of this special investigation indicated that there were no treatment-related changes in sperm characteristics among F_0 animals (information relevant to effects in F_1 animals is not available). Refer to Appendix 1 for details of this study. It was concluded that the equivocal findings of decreased sperm motility noted in the main study were likely due to technical error, and were unrelated to treatment with CGA 293343.

c. Sexual Maturation (F_1): Individual data pertaining to vaginal opening and preputial separation were not included with this submission.

6. Reproductive Performance:

I) **F_0 generation:** Refer to Table 8. There were no treatment-related effects.

Table 8 - Reproductive Performance, F_0 generation[a]

Observations	Dose Group (ppm)				
	Control	10	30	1000	2500
Litter a					
Mean pre-coital interval (days)	5.3	4.9	4	3.7	4.4
Number of females mated (of 30)	28	29	29	26	29
Female mating index, %	93.3	96.7	96.7	86.7	96.7
Number pregnant	25	28	28	23	27
Intercurrent deaths (females)	0	0	1	0	0
Female fertility (pregnancy) index, %	89.3	96.6	96.6	88.5	93.1
Number of males mated (of 30)	28	29	29	26	29
Male mating index, %	93.3	96.7	96.7	86.7	96.7
Male fertility index, %	89.3	96.6	96.6	88.5	93.1
Duration of gestation (days)	22.1	21.8	22.2	22	22
Gestation index, %	100	100	96.4	100	100
Parturition index, %	100	100	96.4	100	100
Number of litters	25	28	27	23	27
Litter b					
Mean pre-coital interval	3.3	3	4.3	4.1	3.2
Number of females mated (of 30)	28	29	29	25	29
Female mating index, %	93.3	96.7	100	83.3	96.7
Number pregnant	24	26	27	22	27
Female fertility (pregnancy) index, %	85.7	89.7	93.1	88	93.1
Number of males mated (of 30)	28	29	29	25	29
Male mating index, %	93.3	96.7	100	83.3	96.7
Male fertility index, %	85.7	89.7	93.1	88	93.1
Duration of gestation (days)	22.2	22	22.1	21.9	22.2
Gestation index, %	100	100	100	100	100
Parturition index, %	100	100	100	100	100
Number of litters	24	26	27	22	27

[a] Data extracted from pages 178 to 180, and pages 198 to 200 of the study report

ii) **F_1 generation:** Refer to Table 9. There were no treatment-related effects.

Table 9- Reproductive Performance, F_1 generation[a]

Observations	Dose Group (ppm)				
	Control	10	30	1000	2500
Litter a					
Mean pre-coital interval (days)	4.2	3.9	4.7	5.4	5.1
Number of females mated (of 30)	30	28	28	30	30
Female mating index, %	100	93.3	93.3	100	100
Number pregnant	28	27	25	26	27
Female fertility (pregnancy) index, %	93.3	96.4	89.3	86.7	90
Number of males mated (of 30)	30	28	28	30	30
Male mating index, %	100	93.3	93.3	100	100
Male fertility index, %	93.3	96.4	89.3	86.7	90
Duration of gestation (days)	22.1	22.2	22	22	22
Gestation index, %	100	100	100	100	100
Parturition index, %	100	100	100	100	100
Number of litters	28	27	25	26	27
Litter b					
Mean pre-coital interval	4	4.2	3.4	2.8	3.2
Number of females mated (of 30)	29	28	23	29	28
Female mating index, %	96.7	93.3	76.7	96.7	93.3
Number pregnant	28	25	21	28	26
Intercurrent deaths, female	0	1	0	0	1
Female fertility (pregnancy) index, %	96.6	89.3	91.3	96.6	92.91
Number of males mated (of 30)	29	28	23	29	28
Male mating index, %	96.7	93.3	76.7	96.7	93.3
Male fertility index, %	96.6	89.3	91.3	96.6	92.9
Duration of gestation (days)	22.2	22.1	22.1	22.1	22.1
Gestation index, %	100	100	100	100	96.2
Parturition index, %	100	100	100	100	96.2
Number of litters	28	25	21	28	25

[a] Data extracted from pages 295 to 297, and pages 313 to 315 of the study report

7. Parental Postmortem Results:

a) Organ Weights:

F_0 generation: There were no treatment-related findings.

F_1 generation: Refer to Table 10. Absolute testis weight was significantly reduced in high-dose males. Absolute thymus weight was reduced in females at 30 ppm and above. Relative thymus weight was reduced in females at 1000 ppm and above. The thymus weight changes were dismissed by the study author on the basis of "comparable" incidence of thymic atrophy in all dose groups (see Table 11 for incidence of thymic atrophy in F_1 females). Although statistically significant, the magnitude of the observed thymus weight changes is slight, and all of the values fall well within range of historical control values, hence no toxicological significance is attached to the thymus weight observations.

Table 10: Absolute and relative organ weight changes in F_1 animals

	Control	10 ppm	30 ppm	1000 ppm	2500 ppm
Absolute testis weight (g)	4.48±0.35	4.42±0.48	4.24±0.37	4.41±0.75	4.08±0.58*
Absolute thymus weight (g, females)	0.32±0.09	0.29±0.07	0.28±0.07*	0.27±0.05**	0.26±0.05**
Relative thymus weight (% bw, females)	0.092±0.025	0.088±0.020	0.081±0.019	0.078±0.015*	0.077±0.015**

Data obtained from study pages286, 290 and 292
* Statistically different from control, $p<0.05$; Dunnett test
** Statistically different from control, $p<0.01$; Dunnett test

b) Pathology

1) Macroscopic Examination:

F_0 generation and F_1 generation: There were no treatment-related findings.

2) Microscopic Examination:

a) **F_0 generation**: Refer to Table 11. **Males:** Findings considered to be treatment-related by the study author were: increased incidence of hyaline changes of renal tubules at 1000 ppm and above; and, increased incidence of renal tubular casts at 2500 ppm. **Females:** There were no findings considered to be related to treatment with CGA 293343.

ii) **F_1 generation**: Refer to Table 11. **Males:** Findings considered to be treatment-related by the study author were: increased incidence of hyaline changes of renal tubules at 1000 ppm and above; and, increased incidence of renal tubular casts at 1000 ppm and above. On examination of the testes of control and high-dose animals, there was an increase in the incidence of tubular atrophy in high-dose animals, therefore testis sections of the intermediate dose groups were examined. The incidence of tubular atrophy (as reported in the original study report) is presented in Table 11. The study author dismissed this finding because it did not show a clear dose-relationship. Subsequent re-examination of testis slides was conducted by the sponsor, and submitted as an amendment to the original study report. Detailed evaluation of the additional information is reported in Appendix 2. In consideration of the information contained in the original report and the re-examination of testis slides as reported in Appendix 2, the incidence and the severity of tubular atrophy in the testes was increased at 30 ppm and above, and is considered by the reviewer to represent a treatment-related effect. **Females:** Hyaline change of renal tubules was noted in one female in the 2500 ppm group, and was considered to be a treatment-related finding by the study author. The study author considered the increased incidence of

thymic atrophy in F_1 females to be within the range of normal biological variation and of no toxicological relevance. Although a dose-related decrease in thymus weight was observed in these animals, the magnitude of the change was slight and well within the range of historical control values. There was no difference in the severity of the thymic atrophy between treated and control animals. In consideration of the above, the slight increase in the incidence of thymic atrophy is probably not related to treatment.

Table 11: Incidence of histopathological changes in F_0 and F_1 animals

	Control	10 ppm	30 ppm	1000 ppm	2500 ppm
F0 generation (No. examined = 30)					
Hyaline change of renal tubules (males)	1	2	3	16	25
Renal tubular casts (males)	22	20	19	23	28
F1 generation (No. examined = 30)					
Hyaline change of renal tubules (males)	3	5	3	24	28
Renal tubular casts (males)	21	20	21	27	29
Tubular atrophy of testes (males)					
Grade 1	4	4	5	9	2
Grade 2	2	3	10	10	10
Grade 3	0	1	0	1	0
Grade 4	0	0	0	2	2
Grade 5	0	0	0	2	0
Total	6	8	15	24	14
Mean severity	1.3	1.6	1.7	2.1	2.1
Thymic atrophy (females)					
Grade 2	7	7	9	10	12
Grade 3	1	1	2	0	0
Grade 4	0	1	0	0	0
Grade 5	0	0	0	0	1
Total	8	9	11	10	13
Mean severity	2.1	2.3	2.2	2.0	2.2
Hyaline change of renal tubules (females)	0	NE	NE	NE	1

Data obtained from pages 17, 37 and 38 of the pathology report (Appendix I.126)
NE = not examined

B. OFFSPRING

1. Clinical Signs: There were no overt clinical signs of treatment-related toxicity in the F_{1a}, F_{1b}, F_{2a} or F_{2b} pups.

2. Viability:

I) **F_0 generation:** Refer to Table 12. Litter parameters were not affected by treatment with CGA 293343.

TABLE 12: Mean Litter Parameters - F_{1a} and F_{1b} litters [a]

Observation	Dose Group (ppm)				
	Control	10	30	1000	2500
Litter a					
Pups Delivered	341	368	357	300	314
Pups Live born	339	363	354	299	309
Live Birth Index	99.4	98.6	99.2	99.7	98.4
Mean Litter Size Day 0	13.6	13.0	13.1	13.0	11.4
Day 4[b]	13.0	12.5	12.9	12.9	11.3
Day 4[c]	7.9	7.9	7.6	8.0	7.7
Day 7	7.8	7.9	7.6	8.0	7.7
Day 14	7.8	7.9	7.6	8.0	7.7
Day 21	7.7	7.9	7.5	8.0	7.7
# Deaths Day 0, %	0.0	0.0	0.0	0.0	0.0
Days 1-4, %	3.8	3.9	1.7	1.0	1.6
Days 5-7, %	0.6	0.0	0.0	0.0	0.0
Days 8-14, %	0.0	0.3	0.0	0.0	0.0
Days 15-21, %	0.6	0.0	0.3	0.0	0.3
Viability Index	96.2	96.1	98.3	99.0	98.4
Lactation Index	98.0	99.5	99.5	100.0	99.5
Sex Ratio (% ♂s, day 0)	48.4	49.6	46.3	50.2	52.4
Litter b					
Pups Delivered	333	360	360	305	330
Pups Live born	332	355	356	293	327
Live Birth Index	99.7	98.6	98.9	96.1	99.1
Mean Litter Size Day 0	13.8	13.7	13.2	13.3	12.1
Day 4[b]	13.0	13.3	12.9	13.7	11.6
Day 4[c]	7.6	7.8	7.6	8.0	7.6
Day 7	7.5	7.8	7.5	7.9	7.6
Day 14	7.5	7.8	7.5	7.9	7.5
Day 21	7.4	7.8	7.5	7.9	7.5
# Deaths Day 0, %	0.0	0.0	0.0	0.0	0.0
Days 1-4, %	5.7	2.3	2.2	1.7	4.3
Days 5-7, %	0.3	0.0	0.3	0.3	0.3
Days 8-14, %	0.6	0.0	0.0	0.0	0.6
Days 15-21, %	0.3	0.0	0.0	0.0	0.0
Viability Index	94.3	97.7	97.8	98.3	95.7
Lactation Index	97.8	100.0	99.5	99.4	98.5
Sex Ratio (% ♂s, day 0)	50	52.1	48.6	45.1	53.5

[a] Data extracted from pages181 to 184 and 201 to 204 of the study report.
[b] Before standardization (culling)
[c] After standardization (culling)
* Statistically different from control, $p<0.05$

ii) **F_1 generation:** Refer to Table 13. Litter parameters were not affected by treatment with CGA 293343.

TABLE 13: Mean Litter Parameters - F_{2a} and F_{2b} litters [a]

Observation	Dose Group (ppm)				
	Control	10	30	1000	2500
Litter a					
Pups Delivered	387	364	348	359	351
Pups Live born	386	358	341	354	351
Live Birth Index	99.7	98.4	98	98.6	100
Mean Litter Size Day 0	13.8	13.3	13.6	13.6	13.0
Day 4[b]	13.4	13.3	13.2	13.5	12.7
Day 4[c]	7.8	7.9	7.8	8.0	7.8
Day 7	7.8	7.9	7.8	8.0	7.8
Day 14	7.8	7.9	7.8	8.0	7.8
Day 21	7.8	7.9	7.8	8.0	7.8
# Deaths Day 0, %	0.0	0.0	0.0	0.0	0.0
Days 1-4, %	2.6	3.4	3.2	0.8	2.3
Days 5-7, %	0.3	0.3	0.0	0.0	0.0
Days 8-14, %	0.0	0.0	0.0	0.0	0.0
Days 15-21, %	0.0	0.0	0.0	0.0	0.0
Viability Index	97.4	96.6	96.8	99.2	97.7
Lactation Index	99.5	99.5	100.0	100.0	100.0
Sex Ratio (% ♂s, day 0)	47.4	49.4	45.5	52	46.2
Litter b					
Pups Delivered	396	360	301	387	353
Pups Live born	395	346	296	385	348
Live Birth Index	99.7	96.1	98.3	99.5	98.6
Mean Litter Size Day 0	14.1	13.8	14.1	13.8	13.9
Day 4[b]	13.7	13.7	13.9	13.3	13.2
Day 4[c]	7.8	7.9	7.9	7.7	7.7
Day 7	7.8	7.9	7.9	7.7	8.0
Day 14	7.8	7.9	7.9	7.7	7.9
Day 21	7.8	7.9	7.9	7.7	7.9
# Deaths Day 0, %	0.0	2.3	0.0	3.1	0.0
Days 1-4, %	3.0	2.9	1.4	3.4	4.9
Days 5-7, %	0.0	0.0	0.0	0.3	0.6
Days 8-14, %	0.3	0.0	0.0	0.3	0.3
Days 15-21, %	0.0	0.0	0.0	0.0	0.0
Viability Index	97.0	94.8	98.6	93.5	95.1
Lactation Index	99.5	100.0	100.0	99.0	98.4
Sex Ratio (% ♂s, day 0)	50.4	51.2	47	44.7	52.3

[a] Data extracted from pages 287 to 300 and 316 to 319 of the study report.
[b] Before standardization (culling)
[c] After standardization (culling)
* Statistically different from control, $p<0.05$
** Statistically different from control, $p<0.01$

3. Body Weight:

I) **F_0 generation:** Refer to Table 14. Mean pup weights were comparable among the control and treatment groups on days 1, 4 and 7 post partum.

On day 14, mean pup weight was slightly lower in the 2500 ppm group for F_{1a} males only (i.e., ~7% lower than control group value).

On day 21, mean pup weight was slightly lower in the 2500 ppm group, for F_{1a} and F_{1b} pups, both sexes (i.e., ~ 8% to 10% lower than control group values).

Overall pup body weight gain was slightly lower in the 2500 ppm group, for F_{1a} and F_{1b} pups, both sexes (i.e., ~ 9% to 12% lower than control group values).

Since the above-noted mean body weight and body weight gain changes, although slight, were up to 12% lower than the concurrent control group values by day 21, and were statistically significant, they were considered to be toxicologically significant by the study author and the reviewer.

TABLE 14: Selected Mean Pup Body Weights (g), F_{1a} and F_{1b} litters [a]

Observation	Dose Group (ppm)				
	Control	10	30	1000	2500
Litter a					
Day 0, ♂s	6.4±0.5	6.1±0.6	6.3±0.6	6.3±0.5	6.3±0.4
♀s	5.9±0.5	5.7±0.5	6.0±0.6	5.9±0.5	5.9±0.5
Day 4[b], ♂s	9.4±1.1	9.2±0.9	9.6±1.3	9.4±0.9	9.6±1.0
♀s	8.9±1.3	9.0±0.7	9.4±1.3	9.0±1.0	9.2±1.1
Day 7, ♂s	15.1±1.8	14.7±1.4	15.3±1.7	15.1±1.3	14.8±1.4
♀s	14.3±2.0	14.5±1.0	15.0±1.8	14.5±1.4	14.4±1.4
Day 14, ♂s	31.2±2.8	30.0±2.6	30.9±2.8	30.3±2.8	29.1±2.6*
♀s	29.9±3.2	29.5±2.1	30.6±3.0	29.3±2.3	28.7±2.5
Day 21, ♂s	54.5±5.2	51.7±4.5	53.5±5.2	52.6±5.2	49.1±4.3**
♀s	51.9±5.0	50.2±3.9	51.6±4.6	50.3±4.3	47.9±4.0**
Mean weight gain (g) Days 0-21, ♂s	48.0±5.1	45.6±4.3	47.3±4.9	46.4±5.0	42.8±4.2**
♀s	46.0±4.7	44.4±3.8	45.6±4.3	44.4±4.2	42.0±3.9**
Litter b					
Day 0, ♂s	6.3±0.8	6.2±0.5	6.4±0.7	6.1±0.4	6.2±0.6
♀s	5.9±0.7	5.8±0.6	6.0±0.8	5.7±0.5	5.9±0.5
Day 4[b], ♂s	9.4±1.8	9.3±0.8	9.3±1.2	9.5±0.8	8.9±1.6
♀s	9.2±1.8	8.8±0.7	9.0±1.3	9.1±1.0	8.6±1.2
Day 7, ♂s	14.9±2.5	15.5±1.2	15.1±1.5	15.4±1.2	13.9±2.8
♀s	14.4±1.8	14.7±1.2	14.5±1.8	14.9±1.3	13.4±2.1
Day 14, ♂s	31.2±4.2	31.4±2.5	30.7±2.6	31.2±2.4	29.1±2.6*
♀	29.9±3.8	29.9±3.1	29.9±2.8	30.6±2.3	27.7±2.9*
Day 21, ♂s	53.6±7.4	53.8±4.0	52.9±4.7	54.0±4.6	48.9±4.5**
♀s	51.7±6.0	50.2±3.5	50.7±5.0	51.7±4.3	46.1±4.9**
Mean weight gain (g) Days 0-21, ♂s	47.3±6.9	47.6±3.9	46.5±4.5	47.9±4.5	42.6±4.3**
♀s	45.8±5.7	44.4±3.6	44.7±4.6	46.0±4.4	40.2±4.7**

[a] Data extracted from pages187 to 192 and 207 to 212 of the study report.
[b] After standardization (culling)
* Statistically different from control, $p<0.05$
** Statistically different from control, $p<0.01$

ii) **F_1 generation:** Refer to Table 15. Mean pup weights were comparable among the control and treatment groups on days 1 and 4 post partum. On day 7, mean pup weight was slightly lower in the 1000 and 2500 ppm groups for F_{2a} females only (i.e., ~ 7% and 9% lower than the control group values, respectively). On day 14, mean pup weight was slightly lower in the 1000 and 2500 ppm groups for F_{2a} females only (i.e., ~6% and 9% lower than control group values, respectively). On day 21, mean pup weight was slightly lower in the 2500 ppm group, for F_{2a} pups, both sexes (i.e., ~ 10% lower for males and 11% lower for females, compared to control group values, respectively) and for F_{2b} pups, both sexes (i.e., ~9% lower for males and 7% lower for females, compared to control group values, respectively); and in the 1000 ppm group, F_{2a} and F_{2b} female pups only (i.e., ~7% lower and 8% lower than control group values, respectively).

Overall pup body weight gain was slightly lower in the 2500 ppm group, for F_{2a} pups, both sexes (i.e., ~ 11 % lower for males and 12 % lower for females, compared to control group values) and for F_{2b} pups, both sexes (i.e., ~10% lower for males and 8% lower for females, compared to control group values, respectively); and in the 1000 ppm group, F_{2a} and F_{2b} female pups only (i.e., ~ 7 % lower and 8% lower than control group values, respectively).

The above-noted mean body weight and body weight changes for males and females in the 2500 ppm group, although slight, were up to 12% lower than the control group values by day 21, and were statistically significant. They were therefore considered to be toxicologically significant by the study author and the reviewer. However, the lower mean body weight noted in the 1000 ppm group, which was considered to be toxicologically significant by the study author, was only up to 8% lower than the control value by day 21, was evident for females only, and a similar effect was not evident for F_0 generation pups in the 1000 ppm group. Hence, although statistically significant, this was not considered to be a toxicologically significant finding by the reviewer.

TABLE 15: Selected Mean Body Pup Weights (g), F_{2a} and F_{2b} litters [a]

Observation	Dose Group (ppm)				
	Control	10	30	1000	2500
Litter a					
Day 0, ♂s	6.5±0.6	6.4±0.6	6.2±0.7	6.3±0.5	6.4±0.5
♀s	6.1±0.6	5.9±0.6	5.8±0.5	5.9±0.4	5.9±0.5
Day 4[b], ♂s	9.6±1.0	9.5±1.0	9.0±1.2	9.3±1.0	9.2±1.5
♀s	9.4±1.0	9.2±0.9	8.9±0.7	8.8±1.1	8.7±1.6
Day 7, ♂s	15.6±1.2	15.1±1.3	14.6±2.3	15.0±1.6	14.7±2.0
♀s	15.4±1.2	14.8±1.4	14.4±1.2	14.3±1.7*	14.0±2.4**
Day 14, ♂s	31.7±2.0	30.7±2.7	30.4±3.9	30.4±2.4	29.5±3.4
♀s	31.3±2.2	30.0±2.4	29.9±2.3	29.4±2.7*	28.4±3.7**
Day 21, ♂s	55.4±3.5	52.9±4.5	52.9±7.2	52.4±4.3	49.9±5.9**
♀s	53.4±3.2	51.0±4.1	51.0±4.7	50.0±4.7*	47.6±5.8**
Mean weight gain (g) Days 0-21, ♂s	48.9±3.4	46.6±4.5	46.7±6.7	46.1±4.1	43.6±5.8**
♀s	47.3±3.1	45.1±4.0	45.1±4.5	44.1±4.5*	41.7±5.5**
Litter b					
Day 0, ♂s	6.4±0.5	6.2±0.5	6.3±0.6	6.3±0.6	6.4±0.4
♀s	6.1±0.5	5.9±0.5	5.9±0.6	5.8±0.5	6.0±0.6
Day 4[b], ♂s	9.5±1.3	9.5±0.9	9.5±1.6	9.3±1.2	8.8±1.5
♀s	9.1±1.3	9.2±0.9	9.2±1.4	8.7±1.4	8.8±1.5

Day 7, ♂s	15.5±1.8	15.2±1.5	15.6±2.2	15.0±1.5	14.2±2.4
♀s	15.0±1.8	14.9±1.2	15.0±1.7	14.1±2.3	14.0±2.5
Day 14, ♂s	32.5±2.4	31.8±2.3	31.8±2.9	31.1±2.5	30.7±4.4
♀s	31.6±2.5	31.3±1.9	31.2±2.8	29.3±4.5	30.0±4.2
Day 21, ♂s	57.8±4.7	55.9±3.8	55.5±4.9	54.6±4.5	52.7±7.2*
♀s	55.1±4.7	54.1±3.0	54.1±4.7	50.9±7.6*	51.3±7.0
Mean weight gain (g)					
Days 0-21, ♂s	51.3±4.4	49.7±3.6	49.2±4.6	48.2±4.2	46.3±7.0**
♀s	49.1±4.4	48.1±2.9	48.1±4.5	45.1±7.5*	45.3±6.7*

[a] Data extracted from pages303 to 308 and 323 to 327 of the study report.
[b] After standardization (culling)
* Statistically different from control, $p<0.05$
** Statistically different from control, $p<0.01$

4. Physical/Behavioural Landmarks: There were no treatment-related effects on eye opening or righting reflex for pups in the F_{1a}, F_{1b}, F_{2a} or F_{2b} litters.

5. Offspring Postmortem Results:

a) Organ Weights: Organ weight data were not included in this submission.

b) Pathology

1) Macroscopic Examination: There were no treatment-related effects for pups in the F_{1a}, F_{1b}, F_{2a} or F_{2b} litters.

2) Microscopic Examination: Microscopic examination was not conducted on any offspring in the F_{1a}, F_{1b}, F_{2a} or F_{2b} litters.

III. DISCUSSION

A. Investigators' Conclusions: The study authors concluded that continuous exposure to the test substance CGA 293343 Technical, admixed to feed at nominal concentrations of 0, 10, 30, 1000 and 2500 ppm resulted in the following treatment-related effects:

> At 2500 ppm, reduced food consumption and retarded body weight gain in parental male rats at 2500 ppm; reduced body weight gain in pups of both sexes in both matings of the F_0 and F_1 generation; an increased incidence of minimal to moderate hyaline change in renal tubules in male F_0 and F_1 animals, and in 1 of 30 F_1 females; and an increased incidence of renal tubular casts (minimal to slight) in male F_0 and F_1 animals.
> At 1000 ppm, reduced body weight gain of F_2 pups (females only); and an increased incidence of minimal to moderate hyaline change and casts in renal tubules in F_1 males.

The study authors concluded that "On the basis of these results, the no observable effect level (NOEL) for CGA 293343 Technical was considered to be 30 ppm in both sexes (equal to approximately 1.3 to 6.4 mg/kg body weight/day; based on the standard conversion factor of 20, this feeding level of 30 ppm is equivalent to a dose of 1.5 mg kg body weight). The corresponding NOAEL was 30 ppm for males and females."

Based on these same data, the sponsor concluded that "Novartis Crop Protection Canada Inc. believes that it is inappropriate to reduce the NOEL in females based on an effect in the pups and that the NOELs should be reported as follows:

NOEL (males) = 30 ppm = range of 1.3 - 4.3 mg/kg bw/day
NOEL (females) = 1000 ppm = range of 59.3 - 219.6 mg/kg bw/day
NOEL (off-spring) = 30 ppm = range of 1.3 - 6.3 mg/kg bw/day."

B. Reviewer's Discussion: A two-generation reproduction study was conducted using Tif: RAI f (SPF) rats, fed test diets containing CGA 293343, purity 98.6%, at dietary concentrations of 0, 10, 30, 1000 and 2500 ppm (equal to 0, 0.61, 1.84, 61.25 and 158.32 mg/kg bw/day for males, and 0, 0.80, 2.37, 79.20 and 202.06 mg/kg bw/day for females), continuously throughout the study period, 30 rats per sex per group. Each female in each generation was mated to produce two litters.

For the parental animals, body weight gain was slightly lower in the 2500 ppm group during the first 6 weeks of the study, F_0 and F_1 generations, males only. However, the effect was marginal, i.e., in the F_0 generation, final body weight and body weight gain were lower by 6 and 8% of the control group values, respectively; and in the F_1 generation, final body weight and total body weight gain were comparable to the control group values. Hence, these body weight changes were not considered to be toxicologically significant. Decreased testis weight was observed in the F_1 generation at 2500 ppm, and increased incidence and severity of tubular atrophy was observed in the testes in the F_1 generation at 30 ppm and above. Sperm motility was decreased in all treatment groups in both generations, however, there was no dose-response relationship, there was high variability among all groups and there were no treatment-related effects on sperm count or sperm morphology. A separate, complementary study was conducted to investigate this finding. On the basis of the special investigation, it was concluded that the initial findings were likely due to technical error and not related to treatment with CGA 293343. The supplemental information was limited to analysis of F_0 animals, hence no information relevant to the findings in F_1 animals is available. Increased incidence of hyaline changes was observed in the renal tubules for F_0 and F_1 males in the 1000 and 2500 ppm groups, and an increased incidence of renal tubular casts was noted for F_0 males in the 1000 ppm group and F_0 and F_1 males 2500 ppm group. Hyaline change in renal tubules was also observed in one F_1 female at 2500 ppm. A slight increase in food consumption for F_1 females during gestation with F_{2a} and F_{2b} litters, but was not considered to be toxicologically significant.

For offspring, body weights were lower in the 2500 pm group, both sexes, by up to 10% of the control group values (F_{1a} and F_{1b} pups on days 14 and/or 21 postpartum; and F_{2a} and F_{2b} pups on days 7, 14 and/or 21 postpartum) and overall body weight gain (i.e., days 1 to 21 postpartum) was lower by up to 12% of the control group value. Slightly lower body weight (days 7, 14 and/or 21) and body weight gain were also noted in the 1000 ppm group, for F_{2a} and F_{2b} females, but was not considered to be toxicologically significant since body weights and body weight gain were only up to 8% lower than the control value by day 21, F_{1a} and F_{1b} pups were not affected and males were unaffected.

There were no adverse, treatment-related effects on reproductive parameters (mating, gestation, fertility, viability) noted at any dose level tested.

Based on the results obtained from this study, the NOAEL for systemic toxicity was determined to be 30 ppm (equal to 1.8 mg/kg bw/day) in males and 2500 ppm (equal to 202 mg/kg bw/day) in females. The NOAEL for offspring was set at 1000 ppm (equal to 61.25 mg/kg bw/day for males, and 79.20 mg/kg bw/day for females). The NOAEL for reproductive toxicity was determined to be 10 ppm (equal to 0.6 mg/kg bw/day) in males and 2500 ppm (equal to 202 mg/kg bw/day) in females.